

ORIGINAL ARTICLE

Toward defining grade C pancreatic fistula following pancreaticoduodenectomy: incidence, risk factors, management and outcome

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Abstract

Background: In 2005 the International Study Group for Pancreatic Fistula (ISGPF) created a definition and grading system for pancreatic fistulae (PF) in which grade C denotes the most severe and potentially life-threatening type. Factors and outcomes associated with grade C fistulae have been ill defined.

Methods: Systematic searches of PubMed and EMBASE were conducted by two independent reviewers utilizing the keywords 'pancreaticoduodenectomy' (PD) and 'pancreatic fistula'. Inclusion criteria were: (i) a sample of ≥ 100 patients; (ii) consecutive accrual of all pathologies, and (iii) use of the ISGPF definition and grading system. Quality appraisal and data extraction were performed using pilot-tested templates.

Results: Fourteen articles describing a total of 2706 PDs met the study entrance criteria. Pancreatic fistulae occurred in 479 patients (18%) and included 71 grade C PF that were directly responsible for 25 deaths (35% mortality rate). Only two studies analysed risk factors; these found soft pancreatic texture and histology other than adenocarcinoma to be the most common risk factors. Ten studies reported management strategies and indicated that 51% of patients required reoperation.

Conclusions: Grade C PF: (i) accounts for 15% of fistulae following PD and has an associated mortality rate of 35%; (ii) occurs most commonly in pathology associated with a soft remnant, and (iii) requires reoperation in approximately one half of patients. The published literature incompletely describes grade C PF.

Keywords

pancreas, neoplasia, resection, morbidity, mortality, outcome

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Introduction

The development of a pancreatic fistula (PF) following pancreaticoduodenectomy (PD) remains common, with reported incidences of 2–25% in the recent literature.^{1–9} This wide variation in incidence largely reflects the historical lack of a universally accepted definition. In 2005, the International Study Group for Pancreatic Fistula (ISGPF) proposed guidelines for consistent stratification which indicated that a PF was defined as present by the drain output of any measurable amount on or after postoperative day 3 with an amylase content greater than three times that of serum.¹⁰ This broad definition includes a spectrum of patients

ranging from the clinically asymptomatic to the critically ill and therefore a grading system (A, B and C) was developed (Table 1). A grade A PF is transient and has no clinical impact. A grade B PF requires a change in management; patients are frequently maintained on a nil by mouth regimen with supplemental nutrition, may require antibiotics and/or therapeutic procedures, and often experience delayed discharge. The most severe grade C PF is associated with a deterioration in clinical status that requires intensive care management. These PF may require reoperation and carry a distinct risk for mortality.

The definition and grading system proposed by the ISGPF was readily accepted by pancreatic surgeons and over the last 5 years

Table 1 Characteristics of grade A, B and C pancreatic fistulae published by Bassi *et al.*¹⁰

	Grade of fistula		
	A	B	C
Clinical condition	Well	Often well	Poor, appears ill
Specific treatment ^a	No	Yes/No	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks) ^b	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to postoperative PF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/No	Yes/No

^aPartial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.

^bWith or without a drain *in situ*.

US, ultrasonography; CT, computed tomography.

has become the predominant classification scheme used in the pancreatic literature. Although numbers of grade C PF are now consistently reported, dramatically different outcomes and mortality rates in the range of 0–40% have been described.^{11,12} Additionally, risk factors and appropriate management strategies for grade C PF have been poorly defined. Thus, a systematic review of the pancreatic surgical literature was performed, firstly to determine the incidence and outcome of grade C PF, and, secondly, to elucidate potential risk factors for the development of PF and surgical management strategies when it occurs.

Materials and methods

Two researchers independently conducted searches of PubMed and EMBASE using the keywords ‘pancreaticoduodenectomy’ and ‘pancreatic fistula’. The results were limited to studies involving adult humans, reported in English, and published during the 5 years (1 August 2005 to 31 July 2010) following the publication of the ISGPF definition. Criteria used for inclusion required that studies: (i) refer to ≥ 100 patients; (ii) demonstrate the consecutive accrual of unselected patients including all pathologic diagnoses, and (iii) show use of the ISGPF definition and grading system. The titles and abstracts of studies that fulfilled these criteria were reviewed and a list was compiled of potential articles. References within these publications were also reviewed to ensure that no salient articles were excluded from this review. Next, the manuscripts of the potentially relevant articles were analysed. Publications that did not meet the inclusion criteria were excluded. If the two reviewers disagreed on whether or not to include a given article, the inclusion criteria were discussed in detail and a unanimous decision was reached. Quality appraisal was performed on all articles that met the inclusion criteria using a pilot-tested template that included data on: first author; year of publication; participating institutions; type of study; study design; corresponding level of evidence; PF definition, and whether PF had been defined and graded by independent

reviewers.¹³ A database was created in which data on the study time period, total number of patients, predominant pathologies, type of reconstruction (pancreaticojejunostomy vs. pancreaticogastrostomy), number of PF, grade of PF, number of deaths from grade C PF, potential risk factors for fistula development and grade C PF operative management were entered for each study.

Results

The PubMed and EMBASE searches yielded 188 references. These included 12 studies in the non-English literature, which were excluded; most of these were small series that would not have met the present entrance criteria. The review of titles and abstracts identified 153 studies that did not meet baseline criteria; these were excluded, leaving 35 potentially relevant manuscripts. The bibliographies of these publications were reviewed to ensure that other pertinent articles were not excluded. No further publications were identified. Of the 35 manuscripts reviewed, 14 were found to fulfil all of the inclusion criteria (Fig. 1).^{11,14–26} The most common reasons for exclusion in the remaining 21 publications were failure to following the ISGPF grading system and/or the exclusion of certain patient populations.

Thirteen articles were observational in design. These included 11 case series^{11,14–17,19,21,23–26} and two cohort studies.^{18,22} One study used an experimental design and was a randomized controlled trial comparing a new pancreaticogastrostomy technique with conventional pancreaticojejunostomy.²⁰ The ISGPF definition and grading system were used in all 14 studies. No articles used independent reviews to identify and grade PF (Table 2).

The studies covered a total of 2706 PDs performed at 18 different institutions across North America, Europe and Asia. The mean duration of the studies reviewed was 5.3 years. The mean number of PDs performed annually was 34. Thirteen of the 14 studies reported the pancreatic anastomotic technique, which involved pancreaticojejunostomy in 1472 cases (73%) and pancreaticogastrostomy in the remainder. Pancreatic fistulae occurred in 479

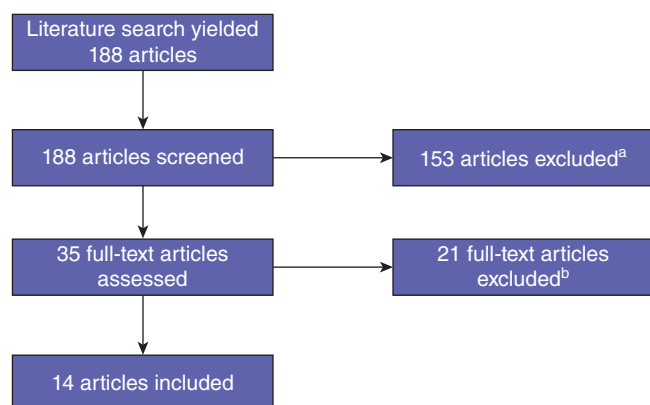


Figure 1 Literature search flow diagram. A total of 174 articles were excluded after review of the abstract^a or full text^b because they failed to meet at least one of the inclusion criteria

Table 2 Articles meeting the inclusion criteria for this review

Authors	Year of publication	Study design	Level of evidence
Akamatsu <i>et al.</i> ²⁵	2010	Case series	IV
Gaujoux <i>et al.</i> ²⁴	2010	Case series	IV
Grobmyer <i>et al.</i> ²³	2010	Case series	IV
Fuks <i>et al.</i> ¹¹	2009	Case series	IV
Kawai <i>et al.</i> ²⁶	2009	Case series	IV
Perwaiz <i>et al.</i> ²²	2009	Cohort study	III
Rosso <i>et al.</i> ²¹	2009	Case series	IV
Fernandez-Cruz <i>et al.</i> ²⁰	2008	Randomized controlled trial	I
Pratt <i>et al.</i> ¹⁷	2008	Case series	IV
Satoi <i>et al.</i> ¹⁸	2008	Cohort study	III
Sledzinski <i>et al.</i> ¹⁹	2008	Case series	IV
Cheng <i>et al.</i> ¹⁵	2007	Case series	IV
Lermite <i>et al.</i> ¹⁴	2007	Case series	IV
Liang <i>et al.</i> ¹⁶	2007	Case series	IV

(18%) patients. Of these PF, 220 (46%) were grade A, 188 (39%) grade B, and 71 (15%) grade C. The overall grade C PF rate was 2.6%. Grade C PF was directly responsible for 25 deaths, equating to a mortality rate of 35%.

Data relevant to potential risk factors and surgical management were also extracted. Only two studies attempted to identify risk factors for grade C PF.^{11,17} Both performed statistical analyses of multiple patient, pancreas and surgery-related factors potentially associated with this complication. One study attempted to identify factors that distinguished grade A and B PF from grade C PF. Univariate analysis showed that perioperative blood transfusion, soft pancreatic texture and postoperative bleeding were associated with grade C PF, but on multivariate analysis only soft pancreatic texture approached significance ($P = 0.06$).¹¹ In the second study, the authors were unable to identify any factors that distinguished

grade C from grade B PF because of the small number of grade C fistulae identified in the study.¹⁷ However, compared with patients with grade A fistulae, those with grade B or C fistulae were statistically more likely to have small duct size, soft gland texture, ampullary, duodenal, cystic or islet cell pathology and increased intraoperative blood loss as determined by multivariate analysis. Details of operative management were included in 10 studies.^{11,14,16,18–21,23,25,26} Twenty-eight of 55 (51%) patients required remedial surgery for a grade C PF. Clear descriptions of the operative technique were given for 26 of the 28 patients: 14 underwent drainage, six underwent anastomotic revision, five underwent completion pancreatectomy, and one underwent a partial pancreatic remnant resection.

Discussion

Pancreatic fistulae remain problematic following elective PD despite advances in surgical technique and perioperative care. With regard to the most severe grade C fistulae, data relative to risk factors for their development, as well as to their operative and non-operative management, have been sparse. Further, outcome measures including factors such as length of stay, delay in functional recovery, delay in initiation of adjuvant therapy, and mortality following these devastating fistulae have been incompletely characterized. The present systematic review of the pancreatic surgical literature identified 14 articles from tertiary referral centres across several countries that met predefined criteria and helped to preliminarily define grade C PF. The findings of this systematic review suggest trends particular to grade C PF and offer a framework for future study.

Pancreatic fistulae are among the most common complications after PD; in this review PF occurred in 18% of patients and it is not uncommon in even the more recent literature.²⁷ Grade C PF, although infrequent, must be anticipated; in the present study it accounted for 15% of all PF and occurred at an overall incidence of 2.6% (range 0–4.9%) in patients undergoing Whipple procedures. A recent survey by 11 high-volume Japanese centres reported an identical incidence of grade C PF.²⁸ By definition, the development of a grade C fistula may lead to death; the mortality rate of 35% identified in this review is not dissimilar to the 39% reported by Fuks *et al.*¹¹ As recent large series from high-volume centres have reported overall mortality rates of <2% following PD, it may be inferred that grade C fistula is a significant contributor to death in many of these patients.^{29,30} These findings suggest that attention should be focused on the aetiology and treatment of this particular complication in an attempt to reduce its incidence. Such a focus might offer an opportunity to significantly reduce the remaining minimal mortality associated with PD.

Risk factors for the development of grade C fistulae in particular have not been well addressed in the literature. Only two of the articles included in this review attempted to elucidate factors associated with these severe fistulae, one of which was inclusive of both grade B and C fistulae.^{11,17} A soft pancreatic remnant, small

duct size, excessive perioperative blood loss and pathology including ampullary, duodenal, cystic and islet cell neoplasms were most often associated with clinically relevant fistulae. Similar observations have been reported by other authors with reference to all PF without stratification to grades A, B or C.^{12,31,32} Kawai and colleagues found that a soft remnant and small duct size were significantly associated with grade B and C fistulae.²⁸ Yeo *et al.* found on both univariate and multivariate analysis that ampullary and duodenal carcinomas were significantly associated with the development of PF.³¹ These trends are not surprising given that these lesions, along with cystic and islet cell neoplasms, infrequently lead to pancreatic duct obstruction or dilation and gland fibrosis, thereby resulting in a soft remnant for reconstruction. Excessive intraoperative blood loss, obesity and a fatty pancreas have also been associated with a higher risk for the development of PF, although the relationships between these factors and grade C fistulae specifically are less well defined.^{17,21,24,28,33}

Most PF can be managed non-operatively, but a significant number of grade C PF do require reoperative surgical intervention. Options include peripancreatic drainage with or without attempted repair of the site of leakage, construction of a new pancreaticoenteric anastomosis, resection of the anastomosis with remnant ligation, and completion pancreatectomy. The most common procedure in this review was peripancreatic drainage with or without attempted repair of the anastomosis, which was performed in over half of all patients. The details contained within the manuscripts were insufficient to elucidate whether any particular procedure yielded superior outcomes. Schlitt and colleagues reported on 31 patients with clinically significant leakage of the pancreatic anastomosis, all but two of whom underwent surgical remediation.³⁴ Ten patients underwent completion pancreatectomy and eight of them died. Sixteen patients underwent either repair of the site of leakage ($n = 8$) or construction of a new anastomosis ($n = 8$); five of these patients died. Finally, in three patients, the anastomosis was excised with either remnant ligation or drainage; two of these patients died. Bachellier *et al.* reported their experience with 12 patients with grade C PF following pancreaticojejunostomy reconstruction, all of whom underwent surgical revision.³⁵ Eight of these patients underwent completion pancreatectomy, with associated mortality of 50%, and four later patients were revised to pancreaticogastrostomy, with no mortality.³⁵ By contrast, van Berg Henegouwen and colleagues, in a series of severe PF, noted the superiority of completion pancreatectomy over either percutaneous or surgical drainage in terms of a reduction in mortality.³² Given the paucity of information relative to treatment specific to grade C PF, optimal management algorithms, both operative and non-operative, relative to these fistulae remain elusive and will require further study.

The outcome of grade C PF deserves special mention. In the present review, the need for reoperation was substantial in common with results in most but not all series.^{12,28,34,35} A total of 35% of patients who developed this complication died, and grade C PF accounted for 41% of all deaths in the 2706 patients

reviewed. Excessive mortality has been noted in other series.^{34,35} This is particularly concerning given that the underlying pathology associated with these fistulae is often associated with more favourable prognoses relative to that of pancreatic adenocarcinoma. A secondary but no less important concern refers to the delay in functional recovery in these patients. Whether they are managed non-operatively or with surgical intervention, grade C PF is uniformly associated with a prolonged hospital stay and greater cost.^{12,30,34} Details of the time to ultimate physical recovery and delay in the institution of adjuvant therapy remain unknown, but a negative impact on both might be anticipated.

There are several limitations to this study. Firstly, systematic reviews are always potentially subject to publication bias. Secondly, the initial literature search brought up 12 articles published in languages other than English, which the present authors were unable to evaluate and thus this review was limited to studies published in English. It is possible that one or two of the articles published in other languages were unfairly excluded, but their inclusion is unlikely to change the present results dramatically. Thirdly, most articles included in this review were retrospective case series and it is possible that the ISGPF definition and grading system were not accurately applied to all patients despite the best efforts of the investigators.

Grade C PF following PD, although uncommon, occurs with a defined incidence and is associated with substantial morbidity, prolonged hospitalization, delayed recovery, and mortality. Many patient-related and operative risk factors for the development of these fistulae have been elucidated. Future progress will require the application of meticulous attention to the recording and reporting of patient-, pancreas- and surgery-related factors associated with these fistulae. It is hoped that clinical trials to evaluate reconstruction strategies or surgical adjuncts that might improve outcomes in this patient population, and strategies for the treatment of PF if it does occur, will evolve.

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Conflicts of interest

None declared.

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